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10/714,567	11/14/2003	Paul Wentworth	1361.028US1	1768

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THE SCRIPPS RESEARCH INSTITUTE
OFFICE OF PATENT COUNSEL, TPC-8
10550 NORTH TORREY PINES ROAD
LA JOLLA, CA 92037

EXAMINER	
VENCI, DAVID J	
ART UNIT	PAPER NUMBER
1641	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/714,567	WENTWORTH ET AL.	
	Examiner	Art Unit	
	David J. Venci	1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *September 2, 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5-13 and 15-44* is/are pending in the application.

4a) Of the above claim(s) *21-44* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5-13 and 15-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-3,5-13 and 15-44* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Examiner acknowledges Applicants' reply filed September 2, 2008. Claims 1, 3, 11 and 13 are amended. Claims 1-3, 5-13 and 15-44 are pending in this application. Claims 21-44 are directed to a non-elected invention and were withdrawn from further consideration pursuant to 37 CFR 1.142(b) in the Office Action dated May 25, 2005.

Claims 1-3, 5-13 and 15-20 are under examination.

This application was filed under 35 U.S.C. § 111(a) on November 14, 2003. This application is a continuation-in-part of 10/380905 filed under 35 U.S.C. § 371 on December 19, 2003, pending, and claims priority under 35 U.S.C. § 119(e) to provision applications 60/426245, filed November 14, 2002, 60/235475, filed September 26, 2000, 60/232702, filed September 15, 2000, and 60/315906, filed August 29, 2001.

Specification

The disclosure is objected to because of the following informalities:

> Throughout the specification, reference to the conversion of "singlet oxygen" into "reactive oxygen species" appears repugnant to the art-recognized definition of "reactive oxygen species" because persons skilled in the art generally do not recognize "singlet oxygen" as a separate genus, but rather recognize that "singlet oxygen" belongs to the broader genus of "reactive oxygen species." Furthermore:

On p. 24, lines 27-28, the phrase "[t]he role of the newly discovered chemical potential of antibodies [to generate reactive oxygen species] *in vivo* is dependent on the availability of the key substrate $^1O_2$*" (paraphrasing mine) is not clear in view of p. 18, lines 4-5 phrase "the term 'reactive oxygen species' means antibody-generated oxygen species". The source of *in vivo* $^1O_2$* is not clear.

On p. 30, line 13, the phrase "[i]n the present invention, the minimum requirements are singlet oxygen, an antibody reagent..." (paraphrasing mine) is not clear in view of p. 18, lines 4-5 phrase "the term 'reactive oxygen species' means antibody-generated oxygen species". The source of *in vivo* $^1O_2$* is not clear.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, 5-13 and 15-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1 and 11, the term "specific" is indefinite because the identity of one or more standards for ascertaining "specific" or "specificity" is not clear. How reactive oxygen is "specific" for anything is not clear.

Claims 3 and 13 do not comply with the requirements of 35 USC 112, second paragraph, for reciting the trademark/trade name "Amplex™ Red". See *Ex parte Simpson*, 218 USPQ 1020 (Bd. App. 1982). The claim scope is unclear because the trademark or trade name does not describe the particular product, but rather identifies its commercial source.

Claim Rejections - 35 USC § 112

New Matter Rejection

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-3, 5-13 and 15-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The specification does not support the following:

1. In claims 1 and 11, detection of administered probes for "reactive oxygen species" which are oxidized by *in vivo* antibody-generated oxygen. With respect to claims 3 and 13, "Amplex Red" was not administered to anything.

2. In claims 1 and 11, a chemical probe "specific" for anything. Applicants' cited portion of the specification p. 30, lines 15-18 does not appear to support this amendment because this portion of the specification does not appear to describe probe-oxygen specificity. The remainder of the specification's usage of the term "specific" appears limited to descriptions of antibody-antigen specificity, or enzyme-substrate specificity.

Applicants are required to cancel new matter in response to this Office Action.

Lack of Enablement

Claims 1-3, 5-13 and 15-20 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.[1] The claims contain subject matter not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 1 requires, *inter alia*, detecting oxidized probes for "reactive oxygen species" (see Specification, p. 18, lines 4-5, "As used herein the term 'reactive oxygen species' means antibody-generated oxygen species"). Claim 1 invokes probes for "reactive oxygen species" which are oxidized by *in vivo* antibody-generated oxygen.

The specification describes *in vitro* detection of probes for "reactive oxygen species" which are *in vitro* oxidized by *in vitro* antibody-generated oxygen. Specifically, the specification teaches:

1. UV-irradiated antibody catalyzes formation of one or more Amplex® Red oxidants (see Fig. 3, □; see *also*, Fig. 7A; see *also*, Fig. 8, ●, Δ, □, ○; see *also*, Figs. 8B, 8C, 8E, 8F and 10B), tris carboxyethyl phosphine oxidants (see Figs. 12A, 12B and 12C, m/z = 265, 267), and indigo carmine oxidants (see Fig. 18B).

2. White light-irradiated hematoporphyrin catalyzes formation of one or more indigo carmine oxidants (see Fig. 19C), especially in the presence of an antibody electron donor (see Fig. 19 B).

[1] According to the decision in *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), the factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of one of ordinary skill; (5) the level of predictability in the art; (6) the amount of direction provided by the inventor; (7) the existence of working examples; and (8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure.

3. UV-irradiated hematoporphyrin catalyzes formation of one or more Amplex® Red hydrogen peroxide products (see Fig. 5, ♦), especially in the presence of an antibody electron donor (see Fig. 5, ●).

The specification does not enable detection methods specific for administered probes for "reactive oxygen species", or specific for administered probes which are oxidized by *in vivo* antibody-generated oxygen. Specifically:

1. The specification provides no direction for performing a method commensurate in scope to the claimed invention. None of the analytical instruments and techniques described in the specification (see *generally*, Specification, p. 24, lines 9-13) were applied to the claimed method for detecting administered probes for "reactive oxygen species", or for detecting administered probes which were oxidized by *in vivo* antibody-generated oxygen. The specification provides no working examples evidencing any of the aforementioned probes (*i.e.*, Amplex® Red, tris carboxyethyl phosphine, indigo carmine) or any of the probes listed in claims 3 or 13 (*i.e.*, vinyl-benzoic acid, indigo carmine, stilbene, cholesterol) being oxidized *in vivo* by antibody-generated oxygen.

2. Prior art antibody-generated "reactive oxygen species" did not have the requisite redox potential *in vivo* to produce detectable oxidized probes. For example, Hewitt *et al.*, 46 ANN. RHEUM. DIS. 866 (1987), discovered that measurements of lipid peroxidation, diene conjugate and fluorescent IgG in exudates (see Figs. 2 and 3) fail to sensitively distinguish between control rats *versus* rats administered UV-irradiated antibodies, suggesting that these antibodies are not catalyzing formation of "reactive oxygen species" to create oxidized probes (*i.e.*, oxidized lipids, dienes and IgGs) to any significant level of detection.

3. Prior art attempts to attribute reactive oxygen generation to antibodies are/were not successful due to background *neutrophil*-generated reactive oxygen. For example, Aaku *et al.*, 1052 BIOCHIM. BIOPHYS. ACTA 243 (1990), discovered that *neutrophils* generate reactive oxygen species, even in the absence of antibodies (see Fig. 2, •), suggesting that antibodies merely cause degranulation of redox mediators that contribute to *neutrophil*-generated reactive oxygen redox processes (see Fig. 2, x).

Based on the foregoing, undue experimentation is necessary to re-make and practice the claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 5, 7-12, 15 and 17-20 are rejected under 35 U.S.C. 102(b) as being anticipated by Hewitt *et al.*, 46 ANN. RHEUM. DIS. 866 (1987).

Hewitt *et al.* describe methods for detecting immunological or inflammatory responses in mammals, the method comprising:

(a) administering a probe to the mammal (see Abstract, second sentence, "A rat model of synovitis was established and challenged with both normal and free radical altered IgG");

(b) obtaining a sample from the mammal (see Abstract, fourth sentence, "reisolation"); and

(c) detecting an oxidized probe in the sample (see Abstract, fourth sentence, "showed the characteristic fluorescence associated with free radical damage");

wherein the oxidized probe indicates peroxyl radicals (see Abstract, fourth sentence, "peroxidation")

Response to Arguments

Claim Rejections - 35 USC § 112

New Matter Rejection

In prior Office Action, claims 1-3, 5-13 and 15-20 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Specifically, claims 1 and 11 require detection of administered probes for "reactive oxygen species" which are oxidized by *in vivo* antibody-generated oxygen. The specification does not describe such detection methods specific for administered probes for "reactive oxygen species" which are oxidized by *in vivo* antibody-generated oxygen.

In response, Applicants argue:

1. the pending claims "only specify administering to a mammal a chemical probe for a reactive oxygen species, obtaining a sample from the mammal, and then detecting an oxidized product of the probe in the sample obtained";

2. the claims do not expressly recite probes that are "oxidized by in vivo antibody-generated" reactive oxygen;

3. the claims are similar in scope to originally filed claims 1 and 11.

Applicants' arguments are not persuasive because the scope of Applicants' arguments is not commensurate to the scope of what is recited in the claims and appears to contradict Applicants' past remarks.

The pending claims encompass administering a chemical probe to a mammal (see *e.g.*, claim 1, "administering to the mammal a chemical probe"), and detecting the "mammal-oxidized" chemical probe (see *e.g.*, claim 1, "wherein detection of the oxidized probe indicates the presence of the reactive oxygen species, thereby detecting an immunological response in the mammal"). Examiner is unable to locate support in the specification for this method.

With respect to 2), *supra*, Applicants' argument appears to contradict Applicants' past remarks where Applicants interpreted their claims as requiring "in vivo antibody-generated" reactive oxygen. For example:

> "Therefore, if the administered probe becomes oxidized, it indicates the presence of one of the recited reactive oxygen species which in turn means there is a immunologicaly response which generates the reactive oxygen species" (see Applicants' reply filed October 19, 2007, p. 10, first paragraph, seventh sentence).

> "The antibodies involved in or activated by an inflammatory response will generate the reactive oxygen species recited in the claims which would catalyze oxidation of the administered probe" (see Applicants' reply filed October 19, 2007, p. 10, first paragraph, tenth sentence).

Clarification is necessary.

Lack of Enablement

In prior Office Action, claims 1-3, 5-13 and 15-20 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

In response, Applicants argue the specification enables the claimed invention because:

1. Skilled persons understand the teachings of Hewitt *et al.*, 46 ANN. RHEUM. DIS. 866 (1987), specifically p. 872, right column, second full paragraph, as supporting a description of IgG-generated reactive oxygen species in vivo (see Applicants' reply, p. 11, first full paragraph, fifth and sixth sentences).

2. Skilled persons understand the teachings of Aaku *et al.*, 1052 BIOCHIM. BIOPHYS. ACTA 243 (1990), as supporting a description of antibody-generated reactive oxygen species on neutrophils in vivo (see Applicants' reply, paragraph bridging pp. 12-13, second sentence).

3. Skilled persons understand the teachings of Hewitt *et al.*, 46 ANN. RHEUM. DIS. 866 (1987), and Aaku *et al.*, 1052 BIOCHIM. BIOPHYS. ACTA 243 (1990), as supporting the scientific accuracy and technical feasibility of antibody-generated reactive oxygen species in vivo (see Applicants' reply, paragraph bridging pp. 12-13, fourth sentence).

With respect to 1) through 3), *supra*, according to M.P.E.P. § 716.01(c), Applicants must factually support any objective evidence with an appropriate affidavit or declaration to be of probative value. As such, Examiner requests Applicants to provide such an affidavit or declaration that, at the very minimal, addresses 1) through 3), *supra*.

Claim Rejections - 35 USC § 102

In prior Office Action, claims 1, 2, 5, 7-12, 15 and 17-20 were rejected under 35 U.S.C. 102(b) as being anticipated by Hewitt *et al.*, 46 ANN. RHEUM. DIS. 866 (1987).

In response, Applicants argue:

1. Hewitt *et al.* describe probes that are not "specific" for any given reactive oxygen species, whereas Applicants' invention requires "specific" probes oxidizable and identifiable by mass spectrometry.

2. Hewitt *et al.* do not teach an "oxidized" chemical probe.

Applicants' arguments have been carefully considered but are not persuasive.

With respect to 1), Examiner reiterates the rejection of claims 1 and 11 under 35 U.S.C. 112 because the term "specific" is indefinite and its definition as applied to probe-oxygen specificity has no support in the specification. Although Applicants' proffered "specificity" definition (*i.e.*, probes that are oxidizable and identifiable by mass spectrometry) has no support in the specification, the specification may support a claim amendment adding one or more steps of detecting oxidizable and identifiable probes by mass spectrometry. Such a proposed claim amendment would appear sufficient to overcome this rejection.

With respect to 2), Hewitt *et al.* detected an oxidized probe (see Abstract, fourth sentence, "IgG which, on reisolation, showed the characteristic fluorescence associated with free radical damage").

Double Patenting

In prior Office Action, claims 1 and 11 were provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 5, 6, 11, 15 and 16 of copending Application No. 10/534574.

In copending Application No. 10/534574, Applicants filed an amendment on September 2, 2008, which cancelled claims 1, 5, 6, 11, 15 and 16. Accordingly, this rejection is withdrawn.

Conclusion

Claims 3, 6, 13 and 16 are free of prior art.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David J. Venci whose telephone number is (571)272-2879. The examiner can normally be reached on 08:00 - 16:30 (EST). If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mark Shibuya can be reached on 571-272-0806. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

David J Venci
Assistant Examiner
Art Unit 1641

/dv/

/Mark L. Shibuya/
Supervisory Patent Examiner, Art Unit 1641